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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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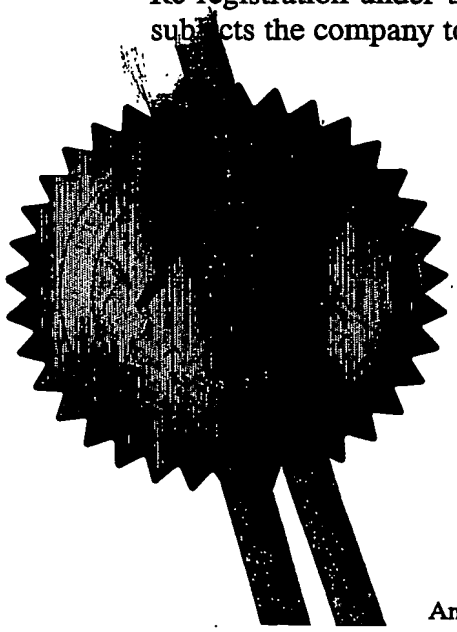

Signed

Dated 17 October 2003

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P01/7700 0.00-0229280.3

Patents Form 1/77

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The **Patent Office**

1/77

Request for grant of a patent

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16 DEC 2002

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1.	Your reference	4-32799P1
2.	Patent application number *(The Patent Office will fill in this part)*	0229280.3
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

Global PM 3/7/3

Novartis Pharmaceuticals UK Ltd
Patents and
Wimblehurst
HORSHAM
West Sussex
RH12

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

Patents Form 1/77

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Continuation sheets of this form	
Description	10 ✓ CF
Claim(s)	5 ✓
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	**One**
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B. A. Yorke & Co.

Date: **16 December 2002**

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mrs. J. Crook**
020 8560 5847

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Notes

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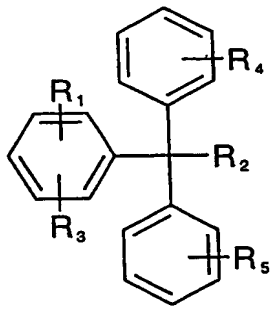
DUPLICATE

Organic Compounds

The present invention relates to a process for preparing organic compounds and to intermediate compounds in such a process.

More particularly, the invention relates to:

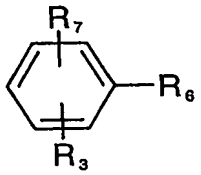
(A) a process for preparing a compound of formula I or a salt thereof



I

wherein R_1 is a reactive substituent or an attachment to a solid phase;
R_2 is a reactive substituent; and
R_3, R_4 and R_5 are each independently hydrogen or one or more substituents attached to each benzene ring, and are selected from hydroxy, amino, C_{1-10}-alkyl, C_{1-10}-alkoxy, C_{1-10}-alkylamino, di-C_{1-10}-alkylamino, carbamoyl, C_{1-10}-alkylcarbamoyl, di-C_{1-10}-alkylcarbamoyl, halo-C_{1-10}-alkyl, halogeno or nitro; comprising

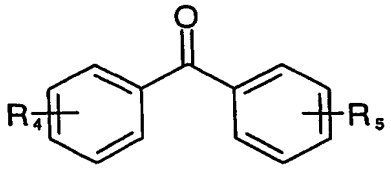
(a) (i) reacting a compound of formula II with a metal or organometallic compound



II

wherein R_6 and R_7 are each a nucleophilic substituent and R_3 is as defined above and is protected if necessary by a removable protecting group; and

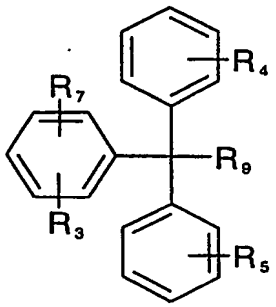
(ii) reacting the compound obtained in (i) with a compound of formula III



III

wherein R_4 and R_5 are as defined above and are protected if necessary by a removable protecting group;

to form a compound of formula V



V

wherein R_3, R_4, R_5 and R_7 are as defined above;

R_9 is –OH, –OM or -OMX, where M is metal and X is a nucleophilic substituent; and

(b) (i) reacting the compound of formula V with a metal or organometallic compound, and

(ii) reacting the compound obtained in (b) (i) with an electrophile, and hydrolysing the resulting compound to form a compound of formula I wherein R_2 is hydroxy;

(c) optionally converting the hydroxy as R_2 to an alternative R_2 group;

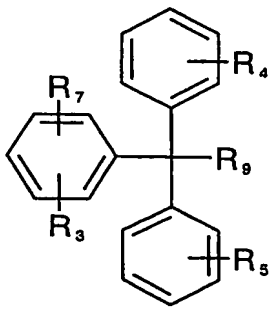
(d) optionally converting R_1 to an alternative R_1 group;

(e) optionally deprotecting a compound of formula I in protected form; and

(e) where required, converting a compound of formula I obtained in free form into the desired salt form, or vice versa;

(B) a process for the preparation of a solid phase support system, comprising preparing a compound of formula I by a process as defined above, and coupling the compound with a suitably derivatised or functionalised solid phase material;

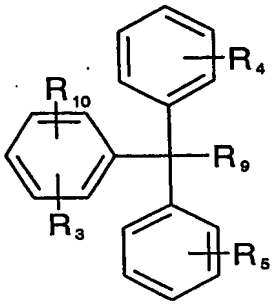
(C) a compound of formula V in free or salt form



V

wherein R_3, R_4, R_5, R_7 and R_9 are as defined above;

(D) a compound of formula VI in free or salt form



VI

wherein R_3, R_4, R_5 and R_9 are as defined above; and
R_{10} is –M or -MX, where M is metal and X is a nucleophilic substituent.

The present invention provides a simple route for the preparation of compounds of formula I, which are useful for solid phase chemical synthesis. The process of the invention may directly produce a compound of formula I attached to a solid phase, or where R_1 is a reactive substituent, the compound of formula I can easily be coupled to a solid phase at a later stage. The presence of the reactive substituent R_2 permits the use of the compounds of formula I as linkers in the synthesis of oligomers and polymers, such as glycopeptides, nucleotides and proteins, especially in the solid phase synthesis of peptides. The compounds of formula I, particularly where R_2 is halogeno, may also be used as protecting agents for protecting functional groups, e.g. amino or hydroxy groups, in chemical synthesis.

The compounds of formula V and VI are useful as intermediate compounds in the preparation of compounds of formula I.

The process of the present invention, for example process steps (a) and (b), may suitably be performed in a single reaction vessel without intermediary isolation.

Terms used in the specification have the following meanings:

"Alkyl" may be straight or branched. Preferably alkyl is C_{1-4}-alkyl.

"Alkoxy" may be straight or branched alkoxy. Preferably alkoxy is C_{1-4}-alkoxy.

"Acylamino" denotes a group of formula –NH-C(O)-R where R is straight chain or branched C_{1-10}-alkyl, cycloalkyl or aryl, for example phenyl. Preferably R is C_{1-4}-alkyl.

"Acyloxy" denotes a group of formula –O-C(O)-R where R is straight chain or branched C_{1-10}-alkyl, cycloalkyl or aryl, for example phenyl. Preferably R is C_{1-4}-alkyl.

"Aryl" is preferably C_{6-10} aryl.

"Halogeno" means fluoro, chloro, bromo or iodo.

"Haloalkyl" means straight chain or branched C_{1-10}-alkyl, substituted by one or more, for example one, two or three halogen atoms, preferably fluorine or chlorine atoms. Preferably haloalkyl is C_{1-4}-alkyl substituted by one, two or three fluorine or chlorine atoms.

"Organometallic compound" denotes a compound in which a carbon atom of an organic group is bound to a metal. The organometallic compound is preferably an alkylmetallic compound, for example an alkyllithium, e.g. a straight or branched chain C_{1-10} alkyllithium compound or may alternatively be an arylmetallic compound, for example an aryllithium. More preferably the alkyllithium compound is a C_{3-5} alkyllithium compound, such as butyllithium.

Alternatively, the organometallic compound may be an organomagnesium compound, for example a straight or branched chain alkylmagnesium or arylmagnesium compound, preferably a C_{1-6} alkylmagnesium compound. Organomagnesium compounds are commonly known as Grignard reagents. The organomagnesium compound is preferably an organomagnesium halide, especially an iodide or bromide.

In further alternative embodiments, the organometallic compound may be an alkyl- or arylzinc compound, for example a C_{1-6}-alkylzinc compound, or an C_{1-6}-alkyl- or aryltin compound.

Where a metal is used, the metal is preferably lithium or magnesium.

R_1 may be a reactive substituent suitable for linking the compound to a solid phase. R_1 may suitably be -C(O)R', -C(O)-OR', -C(O)-NR'R", -R_{12}-NR'R", -R_{12}-OR', -NR'R", or -C(O)X, wherein R' and R" are each independently hydrogen or straight or branched C_{1-10}-alkyl, e.g. C_{1-4}-alkyl, R_{12} is straight or branched C_{1-10}-alkyl, e.g. C_{1-4}-alkyl, and X is a nucleophilic substituent, preferably halogeno, e.g. chloro. R_1 may suitably be in the para, ortho or meta position, preferably in the para position.

Alternatively R_1 may be an attachment to a solid phase material, such as polystyrene. Preferably the attachment is of the formula –C(O)-P, -C(O)-OP, -C(O)-NR'-P, -R_{12}-NR'-P, -R_{12}-OP, -NR'-P, -C(O)-R_{12}-P, -C(O)-OR_{12}-P, -C(O)-NR'-R_{12}-P, -R_{12}-NR'-R_{12}-P, -R_{12}-OR_{12}-P, -NR'-R_{12}-P or –R_{12}-P, wherein R', R" and R_{12} are as defined above and P is a solid phase material. More preferably R_1 is -C(O)-OP, -C(O)-OR_{12}-P, -C(O)-NH-P, -C(O)-NH-R_{12}-P, -NH-R_{12}-P or –R_{12}-P, wherein R_{12} is methyl, e.g. -CH_2-P.

R_2 is preferably a reactive substituent suitable for linking the compound to a biological oligomer or polymer, or a monomer unit thereof, e.g. an amino acid or polypeptide. R_2 may suitably be hydroxy, acylamino, acyloxy, amino, halogeno, sulfhydryl, C_{1-10}-alkoxy or C_{6-10}-aryloxy, preferably halogeno.

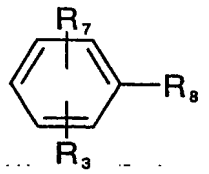
Each benzene ring shown in formulae I to VII may be substituted by one or more groups. For example R_3 may designate one to four substituent groups, preferably one or two substituent groups, attached to the benzene ring shown in formulae I, II and IV to VII. R_4 and R_5 may designate one to five substituent groups, preferably one to three substituent groups, attached to each of the benzene rings shown in formulae I, II and IV to VII. Each substituent group may be present at any suitable position on the benzene rings to which they are attached. More preferably R_4 and/or R_5 is a substituent group at the ortho or para position on the benzene ring to which it is attached.

Each of R_3, R_4 and R_5 may be protected by a removable protecting group if necessary, e.g. when it contains an –OH or –NH_2 group which does not participate in the reaction. Protecting groups, their introduction and removal are described, for example, in "Protective Groups in Organic Synthesis", T. W. Greene et al., John Wiley & Sons Inc., Second Edition 1991. Preferably each of R_3, R_4 or R_5 is a group which does not require protection, e.g any of the groups listed above other than hydroxy, amino or nitro.

When R_3, R_4 or R_5 is halogeno, it is preferably fluoro or chloro. When R_3, R_4 or R_5 is haloalkyl it is preferably trifluoromethyl. Preferably R_3 is C_{1-4}-alkyl, halogeno, or hydrogen. Preferably R_4 and R_5 are each independently C_{1-4}-alkylcarbamoyl, di-C_{1-4}-alkylcarbamoyl, carbamoyl, trifluoromethyl, fluoro or chloro. Preferably R_4 and R_5 are the same.

Preferably the nucleophilic substituents R_6 and R_7 are each independently halogeno, more preferably bromo or iodo, and most preferably R_6 and R_7 are each bromo. R_7 may suitably be in the para, ortho or meta position, preferably in the para position.

In one embodiment of the invention, the compound of formula II is first reacted with the metal or organometallic compound to form a compound of formula IV:



IV

wherein R_3 and R_7 are as defined above and R_8 is –M or –MX, where M is metal and X is a nucleophilic substituent, preferably halogeno.

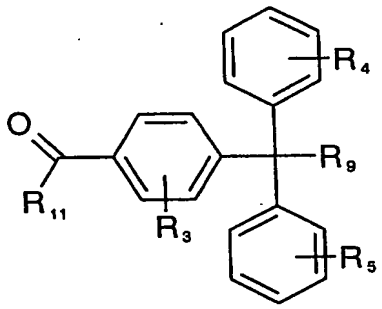
Where the metal is lithium or the organometallic compound is an organolithium compound, R_8 is -Li. Where the metal is magnesium or the organometallic compound is a Grignard reagent, R_8 is –MgX, and X is preferably halogeno. The compound of formula IV is then reacted with a compound of formula III to form a compound of formula V.

The compounds of formulae IV and V need not be separated or isolated but may be prepared *in situ.*

Suitable electrophiles for use in step (b) include carbon dioxide, isocyanates, nitriles, acyl halides (such as phosgene), leading to the formation of, for example, compounds of formula I wherein R_1 is carboxy, carbamoyl, alkylcarbamoyl or acyl. Alternatively the electrophile may be a derivatised solid phase material, e.g. a Merrifield polymer, enabling direct coupling of the compound of formula VI to a solid phase. In one embodiment the electrophile is a compound of formula X'-$(CH_2)_n$-P, wherein X' is a nucleophilic substituent e.g. halogeno or tosyloxy, n is an integer between 1 and 4, preferably 1, and P is a solid phase material.

Where the electrophile is carbon dioxide, step (b) preferably comprises first reacting the compound of formula V with a metal or organometallic compound to form a compound of formula VI as defined above and reacting, preferably in situ, the compound of formula VI with carbon dioxide.

Where the electrophile is carbon dioxide, preferably a compound of formula VII is formed:



VII

wherein R_3, R_4, R_5 and R_9 are as defined above; and
R_{11} is –OH, –OM or -OMX, where M is metal and X is a nucleophilic substituent, preferably halogeno, in salt or free form.

Alternatively, the carboxylation step comprises reacting a compound of formula V with carbon dioxide in the presence of a metal or organometallic compound, to form a compound of formula VII.

The hydrolysis step in b) ii) preferably comprises reacting a compound of formula VII wherein R_{11} is –OM or –OMX and/or R_9 is –OM or –OMX with water or an acid yielding a compound of formula I wherein R_1 is carboxy and R_2 is hydroxy, in salt or free form. Suitable acids include ammonium chloride, acetic acid, sulphuric acid and hydrochloric acid. A pH-buffered solution may also be used. Preferably a weak acid is used and/or the step may be carried out at a pH of 4 to 7. The reaction temperature may conveniently be –50 to 50°C, preferaby –10 to 10°C.

Alternatively the compound of formula VII where R_{11} is –OM or –OMX may be reacted with a a nucleophile, e.g. an amine or halide, to form a compound of formula I wherein R_1 is -C(O)-NR'R" or –C(O)-X and R', R" and X are as defined above.

Step (a) may conveniently be carried out in an inert organic solvent, preferably an ether solvent, for example diethyl ether or tetrahydrofuran. Alternatively a hydrocarbon solvent may be used. The reaction temperature for step (a) is conveniently –30 to –100°C, preferably –50 to –70°C. The reaction may, for example, be carried out using 0.5 to 2 equivalents, preferably 0.8 to 1.2 equivalents and most preferably about 1 equivalent of the metal or organometallic compound per equivalent of the compound of formula II. 0.5 to 2 equivalents, preferably 0.8 to 1.2 equivalents of the compound of formula III may be used per equivalent of the compound of formula II.

Step (b) may conveniently be carried out in an inert organic solvent as above. The reaction temperature may conveniently be –30 to –100°C, preferably –50 to –70°C. Preferably 0.5 to 2 equivalents, more preferably 0.8 to 1.2 equivalents of a metal or organometallic compound per equivalent of the compound of formula V are used.

The groups R_1 and R_2 may be converted to alternative R_1 and R_2 groups specified above by standard processes, such as by esterification, amidation or nucleophilic substitution. For example, a compound of formula I wherein R_2 is hydroxy may be converted to a compound of formula I wherein R_2 is halogeno by reaction with an acyl halide, e.g. acyl chloride.

Preferably the compound of formula I is in free form. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallization.

Compounds of formula I can be recovered from the reaction mixture and purified in a conventional manner.

The starting compounds of formula II or formula III are known or may be prepared by methods analogous to those known in the art. Organometallic compounds may be prepared by standard processes, for example by reaction of an alkyl or aryl halide with a metal, for example lithium or magnesium, suspended in diethyl ether or tetrahydrofuran. The organometallic compound is preferaby prepared and used in an inert (oxygen-free) anhydrous atmosphere, for instance under nitrogen.

The process according to the invention may suitably include a further step of coupling the compound of formula I wherein R_1 is a reactive substituent to a solid phase material. Suitable solid phase materials are disclosed, for example, in DE 4306839 A1, and include naturally occurring or synthetic organic or inorganic polymers in particulate form, e.g. as beads, or preferably as a surface layer on a suitable inert substrate material. Examples of suitable polymer materials include crosslinked polystyrene, e.g. polystyrene pins, Gly-HMD-MA/DMA pins and HEMA pins. The compound of formula I may conveniently be coupled to a solid phase material by reacting a group present on the solid phase with R_1. Preferably a compound of formula I, wherein R_1 is a carboxy group or an activated carboxy group, e.g. as disclosed in the example, is reacted with a polymer bearing free amino groups.

The process according to the invention may also suitably include a further step of coupling the compound of formula I, optionally bound to a solid phase material, to a biological oligomer or polymer, or a monomer unit thereof. The compound may conveniently be coupled to the biological molecule, e.g. an amino acid or polypeptide, by reacting a group present on the biological molecule with R_2. For example, where R_2 is hydroxy and the biological molecule is a polypeptide or amino acid, the terminal carboxylic acid group of the biological molecule can be esterified by the R_2 hydroxy group, optionally via initial reaction of the compound of formula I with an acyl halide leading to *in situ* substitution of hydroxy by halogeno.

The invention will now be described with reference to the following specific embodiments.

Example 1

Preparation of 4-(diphenyl-hydroxy-methyl)-benzoic acid

1,4-dibromobenzene (47.2 g, 0.2 M) is added to tetrahydrofuran (THF, 240 ml). The clear solution is cooled to –65°C. A butyllithium solution (0.22 M, 94 ml of a 20% solution in CHX) is added over 30 minutes.

After 5 minutes of stirring a solution of benzophenone (36.4 g, 0.2 M in 180 ml THF) is added over 30 minutes (exothermic). The mixture is stirred for a further 30 minutes at –65°C. Then over 30 minutes the temperature is raised to –10°C and the solution is stirred at this temperature for one hour.

The reaction mixture is then re-cooled to –65°C. Over 30 minutes a butyllithium solution (0.22 M, 94 ml of a 20% solution in cyclohexane) is added.

The resulting suspension is diluted with 200 ml THF. Then carbon dioxide gas is introduced over 90 minutes at –65°C. The temperature is raised to 20°C and the mixture stirred overnight. The mixture is then cooled to 0°C and an aqueous solution of ammonium chloride (120 ml of a 10% solution) is added over 30 minutes. 4-(diphenyl-hydroxy-methyl)-benzoic acid is formed at this stage.

The mixture is evaporated at 45°C under a vacuum. The residue is adjusted to pH 4 with acetic acid and mixed with 400 ml H_2O. Extraction is performed with 2 x 150 ml ethyl acetate. The organic phases are extracted again with 100 ml water.' The combined EST-phases are shaken with a 10% aqueous potassium hydroxide solution (2 x 120 ml). The combined aqueous phases are adjusted to pH 1-2 with hydrochloric acid at 20°C and then extracted with 2 x 150 ml TBME (tert-butyl methyl ether). The combined TBME phases are mixed with 50 ml water and 50 ml saturated Na_2SO_4, dried with magnesium sulphate and evaporated at 45°C under vacuum to obtain a crude product.

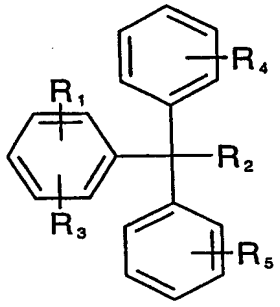
38.3 g crude product is dissolved in TBME (300 ml) at 40°C. The clear yellow solution is concentrated in a volume of 60 ml (240 ml TBME distilled off). The mixture is stirred for one hour at 40°C (crystallisation). 50 ml HPTF is added, the mixture is cooled to 0°C and stirred at 0°C for 1 hour. Evaporating and washing with 2 x 15 ml heptane fraction and drying overnight at 45°C under vacuum gives white crystals.

Attachment of 4-(diphenyl-hydroxy-methyl)-benzoic acid to a solid phase

15g 4-(diphenyl-hydroxy-methyl)-benzoic acid with 7.54 g hydoxybenzotriazole is dissolved in 140 ml dimethylformamide (DMF) by stirring for 15 min. 15.3 ml di-isopropylcarbo-di-imide is added and the solution kept at room temperature for 30 min. The solution is then stirred overnight at room temperature in the presence of aminomethylated polystyrene. After washing with DMF, methanol and THF the linker derivatised support is dried under vacuum.

Claims

1. A process for preparing a compound of formula I or a salt thereof



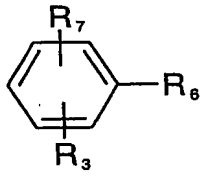
I

wherein R_1 is a reactive substituent or an attachment to a solid phase;

R_2 is a reactive substituent; and

R_3, R_4 and R_5 are each independently hydrogen or one or more substituents attached to each benzene ring, and are selected from hydroxy, amino, C_{1-10}-alkyl, C_{1-10}-alkoxy, C_{1-10}-alkylamino, di-C_{1-10}-alkylamino, carbamoyl, C_{1-10}-alkylcarbamoyl, di-C_{1-10}-alkylcarbamoyl, halo-C_{1-10}-alkyl, halogeno or nitro; comprising

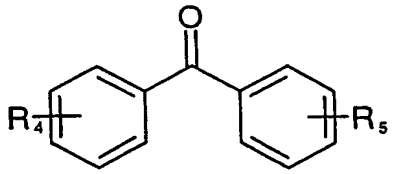
(a) (i) reacting a compound of formula II with a metal or organometallic compound



II

wherein R_6 and R_7 are each a nucleophilic substituent and R_3 is as defined above and is protected if necessary by a removable protecting group; and

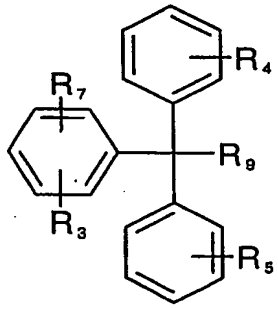
(ii) reacting the compound obtained in (i) with a compound of formula III



III

wherein R_4 and R_5 are as defined above and are protected if necessary by a removable protecting group;

to form a compound of formula V



V

wherein R_3, R_4, R_5 and R_7 are as defined above;

R_9 is –OH, –OM or -OMX, where M is metal and X is a nucleophilic substituent; and

(b) (i) reacting the compound of formula V with a metal or organometallic compound, and

(ii) reacting the compound obtained in (b) (i) with an electrophile, and hydrolysing the resulting compound to form a compound of formula I wherein R_2 is hydroxy;

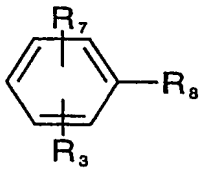
(c) optionally converting the hydroxy as R_2 to an alternative R_2 group;

(d) optionally converting R_1 to an alternative R_1 group;

(e) optionally deprotecting a compound of formula I in protected form; and

(e) where required, converting a compound of formula I otained in free form into the desired salt form, or vice versa.

2. A process according to claim 1, wherein step (a) (i) comprises forming a compound of formula IV



IV

wherein R_3 and R_7 are as defined above and R_8 is –M or –MX, where M is metal and X is a nucleophilic substituent;

and step (a)(ii) comprises reacting the compound of formula IV with the compound of formula III.

3. A process according to claim 1 or claim 2, wherein the organometallic compound comprises an alkyllithium compound.

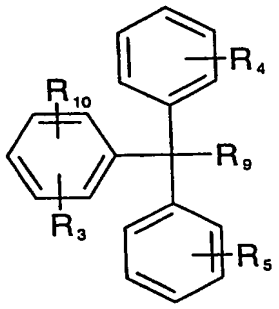
4. A process according to claim 3, wherein the alkyllithium compound comprises butyllithium.

5. A process according to any preceding claim, wherein R_1 is carboxy.

6. A process according to any preceding claim, wherein R_2 is hydroxy.

7. A process according to any preceding claim, wherein R_6 and R_7 are each independently bromo or iodo.

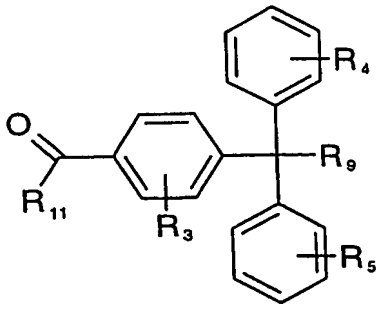
8. A process according to any preceding claim, wherein step (b) comprises
(i) reacting the compound of formula V with a metal or organometallic compound to form a compound of formula VI, in free or salt form:



VI

wherein R_3, R_4, R_5 and R_9 are as defined above; and
R_{10} is –M or -MX, where M is metal and X is a nucleophilic substituent;
and reacting the compound of formula VI with carbon dioxide.

9. A process according to claim 8, wherein step (b) comprises forming a compound of formula VII:



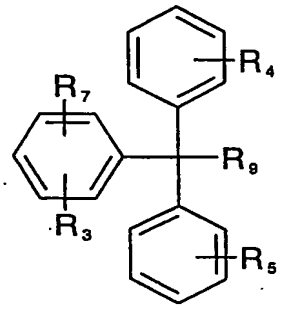
VII

wherein R_3, R_4, R_5 and R_9 are as defined above; and

R_{11} is –OH, –OM or -OMX, where M is metal and X is a nucleophilic substituent, in salt or free form.

10. A process for the preparation of a solid phase support system, comprising preparing a compound of formula I by a process as defined in any of claims 1 to 9, and coupling the compound with a suitably derivatised or functionalised solid phase material.

11. A compound of formula V in free or salt form



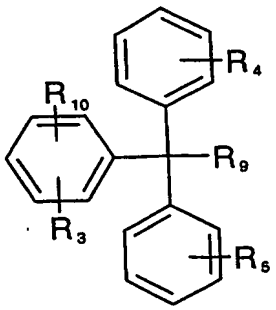
V

wherein R_3, R_4 and R_5 are each independently hydrogen or one or more substituents attached to each benzene ring, and are selected from hydroxy, amino, C_{1-10}-alkyl, C_{1-10}-alkoxy, C_{1-10}-alkylamino, di-C_{1-10}-alkylamino, carbamoyl, C_{1-10}-alkylcarbamoyl, di-C_{1-10}-alkylcarbamoyl, halo-C_{1-10}-alkyl, halogeno or nitro, optionally protected by a removable protecting group;
R_7 is a nucleophilic substituent; and
R_9 is –OH, –OM or -OMX, where M is metal and X is a nucleophilic subtituent.

12. A compound according to claim 11, wherein R_7 is bromo or iodo.

13. A compound according to claim 11 or claim 12, wherein R_9 is -OLi, -OMgBr, -OMgI or –OH.

14. A compound of formula VI in free or salt form



VI

wherein R_3, R_4 and R_5 are each independently hydrogen or one or more substituents attached to each benzene ring, and are selected from hydroxy, amino, C_{1-10}-alkyl, C_{1-10}-alkoxy, C_{1-10}-alkylamino, di-C_{1-10}-alkylamino, carbamoyl, C_{1-10}-alkylcarbamoyl, di-C_{1-10}-alkylcarbamoyl, halo-C_{1-10}-alkyl, halogeno or nitro, optionally protected by a removable protecting group;

R_9 is –OH, –OM or -OMX, where M is metal and X is a nucleophilic subtituent; and

R_{10} is –M or -MX, where M is metal and X is a nucleophilic substituent.

15. A process substantially as hereinbefore described with reference to the example.

16. A compound of formula V or formula VI substantially as hereinbefore described with reference to the example.